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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,071	09/30/2005	Chuan-Yuan Li	180/156 PCT/US	6572

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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,071	LI ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 15-36* is/are pending in the application.

4a) Of the above claim(s) *17-20 and 22-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,15,16 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 19 February 2008.

Claim Status

Claims 1-8 and 15-36 are pending. Claim 1 is amended. Claims 9-14 are cancelled. Claims 17-20 and 22-36 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-8, 15-16, and 21 are under current examination.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 9 January 2008 consisting of 2 sheet(s) is/are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit as a 371 of PCT/US03/31097 (filed 10/01/2003) which claims benefit of 60/415,319 (filed 10/01/2002). The applicant submitted an oath

on 3/24/2005, which was not executed in accordance with there 37 CFR 1.66 or 37 CFR 1.68. The applicant was notified of this in the DO/EO filed 8/1/2005. Since the instant application is a National Stage Application, rather than a standard US non-provisional application, the application was not afforded the filing date 3/24/2005 (when the specification, claims, and drawings were submitted). Rather, the instant application has been granted the filing date of 9/30/2005, which is the date on which a properly executed oath was received. Because receipt of the properly executed oath completed filing of the National Stage application within the 30 month period for filing of the National Stage application of PCT/US03/31097, the instant application has been granted the benefit date, 1 October 2002 from provisional application 60/415,319.

Response to Arguments - Claim Rejections 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-8, 15-16, and 21 remain rejected under 35 USC 102(a/e) as anticipated by Van Meir et al. (WO02/26192).

Applicant's arguments (Remarks, pages 10-14) and claim amendments filed 19 February 2008 have been fully considered but they are unpersuasive.

The applicant argues that Van Meir et al. do not teach each and every limitation of the instant claims. The applicant particularly argues that Van Meir do not teach the newly added limitations directed to "an adenovirus gene and a transgene, each under the transcriptional control of a TRE" and "wherein the transgene is a suicide gene." The applicant also discusses his view of suicide genes (pages 12-13).

Contrary to the applicant's assertion, Van Meir et al. teach each and every limitation of the instant claims. In particular, Van Meir et al. teach the limitations regarding both genes under the transcriptional control of hypoxia response elements, "recombinant viruses can be further engineered so that the number of genes expressed is increased to four if internal ribosomal entry sites (IRES) are used to express two genes per transcription unit. According to this embodiment, a plurality of genes can be expressed in response to hypoxia" (page 20, lines 2-5). In regard to suicide genes, Van Meir et al. teach "molecular strategy underlying the design of virus mediated gene therapy systems is to deliver a gene which will inhibit tumor cell growth (e.g., controlling cell cycle or apoptosis), kill the cell (suicide gene), or induce an immune response (immunotherapy)." (page 2, lines 16-18). The amended claim 1 indicates that suicide genes include HSV-tk; Van Meir et al. teach recombinant viruses of the invention can be further engineered to contain a gene such as thymidine kinase (page 19, lines 28-29

through page 20, line 1).As the applicant is well aware, thymidine kinase (tk) functions to kill cells by converting ganciclovir to a toxic nucleotide analog (Specification, page 35, lines 30-31). Therefore, the examiner considers the applicant's arguments unpersuasive.

Claim 1 is directed to an adenovirus vector comprising an adenovirus gene under the transcriptional control of a transcriptional regulatory element (TRE) comprising a minimal promoter and a hypoxia responsive element (HRE). Van Meir et al. teach, "a recombinant virus genetically engineered to have an hypoxia-responsive element, or a multiplicity of such elements, operably linked to a promoter which is operably linked to a gene or genes which regulate or modulate replication of the virus or encode a therapeutic molecule." (page 7, lines 18-21). Van Meir et al. further describe the recombinant virus as "a recombinant replication-competent adenovirus" and "an hypoxia/HIF-dependent replicative adenovirus" (page 9, lines 10 and 13). Van Meir et al. teach, "Thus this E1A gene of an adenovirus (or any structural or functional homolog) may be engineered to be put under the control of an hypoxia responsive element/promoter, thus creating an organism that selectively replicates under hypoxic conditions." (page 18, lines 7-10). Van Meir et al. teach an adenovirus "containing the CMV minimal promoter and the E1 gene" (page 12, line 1). See diagram of Example 4, on pages 27-28, for a more visual representation of the arrangement of elements taught by Van Meir et al. comprising HRE and minimal promoter controlling expression of E1 gene.

Claim 2 is directed to the adenovirus vector of claim 1, wherein the adenovirus gene is selected from the group consisting of an E1A gene, an E1B gene, an E2A gene, an E2B gene, and an E4 gene. Van Meir et al. teach, "Thus this E1A gene of an adenovirus (or any structural or functional homolog) may be engineered to be put under the control of an hypoxia responsive element/promoter, thus creating an organism that selectively replicates under hypoxic conditions." (page 18, lines 7-10).

Claim 3 is directed to the adenovirus vector of claim 1, further comprising a second adenovirus gene under the transcriptional control of the TRE. Van Meir et al. teach, "recombinant adenoviruses were able to express constitutively (Ad-CMV-E1) or conditionally (HYPR-Ad1) E1A and E1B gene products. " (page 34, lines 1-2). See also Figure 6.

Claim 4 is directed to the adenovirus vector of claim 1, wherein the minimal promoter is selected from the group consisting of the cytomegalovirus (CMV) minimal promoter, the human β-actin minimal promoter, the human EF2 minimal promoter, and the adenovirus E1B minimal promoter. Van Meir et al. teach an adenovirus "containing the CMV minimal promoter and the E1 gene" (page 12, line 1).

Claim 5 is directed to the adenovirus vector of claim 4, wherein the CMV minimal promoter comprises SEQ ID NO: 1. Van Meir et al. teach an adenovirus "containing the CMV minimal promoter" (page 12, line 1).

Claim 6 is directed to the adenovirus vector of claim 1, wherein the HRE is derived from the human vascular endothelial growth factor (VEGF) promoter. Van Meir

et al. teach, "based on this information, EPO and VEGF HRE's were chosen for the design and testing of a hypoxia-responsive promoter" (page 19, lines 1-2).

Claim 7 is directed to the adenovirus vector of claim 6, wherein the HRE comprises SEQ ID NO: 2. Van Meir et al. teach "the VEGF [HRE] sequence... CCACAGTGC TACGTGGGCT CCUCAGGTC CTCTT" which is 100% identical to SEQ ID NO:2 of the instant application.

Claim 8 is directed to the adenovirus vector of claim 7, wherein the HRE comprises five tandem copies of SEQ ID NO: 2. See Van Meir et al., Figure 2, where up to 6 tandem copies of HRE are shown and page 10-11 for detailed description of figure.

Claim 9 is directed to the adenovirus vector of claim 1, further comprising a transgene. Van Meir et al. teach that their adenoviruses express anti-angiogenic factors (page 13, lines 23-26, and page 15, lines 10-15).

Claim 10 is directed to the adenovirus vector of claim 9, wherein the transgene is a second adenovirus gene. Van Meir et al. teach, "recombinant adenoviruses were able to express constitutively (Ad-CMV-E1) or conditionally (HYPR-Ad1) E1A and E1B gene products." (page 34, lines 1-2).

Claim 11 is directed to the adenovirus vector of claim 9, wherein the transgene encodes an immunostimulatory molecule. Meir et al. teach "genes which can be used in the invention include...IL-12" (page 23, lines 8-14).

Claim 12 is directed to the adenovirus vector of claim 11, wherein the immunostimulatory molecule is selected from the group consisting of IL2 and IL12. Van

Meir et al. teach "genes which can be used in the invention include…IL-12" (page 23, lines 8-14).

Claim 13 is directed to the adenovirus vector of claim 9, wherein the transgene is a suicide gene. Van Meir et al. teach, "Recombinant viruses of the invention can be further engineered to contain a gene that allows for the termination of viral propagation with an exogenous agent, such as thymidine kinase, which would render them susceptible to ganciclovir." (page 19, lines 28-29 through page 20, line 1).

Claim 15 is directed to a composition comprising the adenovirus vector of claim 1. Van Meir et al. teach, "compositions of the invention comprise a recombinant virus genetically engineered to have an hypoxia-responsive element, or a multiplicity of such elements, operably linked to a promoter which is operably linked to a gene or genes which regulate or modulate replication of the virus or encode a therapeutic molecule." (page 7, lines 18-21).

Claim 16 is directed to the composition of claim 15, further comprising a pharmaceutically acceptable carrier. Inherently, any aqueous solution of the adenoviral composition of claim 15 would be a pharmaceutically acceptable carrier.
Claim 21 is directed to a host cell comprising the adenovirus vector of claim 1. Van Meir et al. teach, "expression of recombinant viral gene products in transfected cells under hypoxic and normoxic conditions…. adenoviruses, U251MG and LN-229 cells were infected with the Ad-CMV-E1 and HYPR-Ad1" (page 33, lines 17-29).

Accordingly, Van Meir et al. anticipated the instant claims.

Therefore, the examiner hereby maintains the rejection of claims 1-8, 15-16, and 21 under 35 USC 102(a/e) as anticipated by Van Meir et al. (WO02/26192) for the reasons of record and the comments above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Janet L. Epps-Ford/

Primary Examiner, Art Unit 1633

/SDL/ Scott Long
Patent Examiner, Art Unit 1633